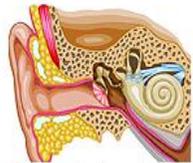


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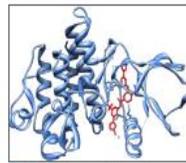
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14th World Congress on Gastrointestinal Cancer (WCGC)

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Simple Way to Avoid Severe Toxicity From 5-FU and Related Drugs

Zosia Chustecka

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July 5, 2012 — A simple screening process can identify people who will react badly to the fluoropyrimidine group of chemotherapy drugs, which includes 5-fluorouracil and the related oral products capecitabine (*Xeloda*), tegafur, and S-1.

In some cases, this prescreen is life-saving, say the French researchers who developed the method. They reported study details in an oral poster presentation at the 14th World Congress on Gastrointestinal Cancer, which was organized in partnership with the European Society for Medical Oncology and held in Barcelona, Spain.

Drugs in the fluoropyrimidine group are widely used in the treatment of many different types of cancer, including colorectal and breast cancer, said Jean-Philippe Metges, MD, from CHU Hôpital Morvan in Brest, France. However, these drug carry a risk of early severe toxicity (seen in about 25% of patients after the first cycle) and even death as a result of severe toxicity (in about 0.4% to 0.6% of patients, which amounts to some 1300 patients per year in the United States).

The toxic reaction is related to an asymptomatic deficiency of the dihydropyrimidine dehydrogenase (DPD) enzyme, Dr. Metges explained. People who have a complete DPD deficiency — which is rare — suffer multiorgan toxicity, which can be fatal; in these people, fluoropyrimidine drugs should be avoided. In people with the more common partial DPD deficiency, the drugs can be used but at reduced doses to reduce the risk of toxic effects, he said.

Currently, there is some screening being carried out for the genetic mutations responsible for DPD deficiency, but it does not identify all patients who are at risk, Dr. Metges pointed out.

The screen developed by researchers at the Institut de Cancérologie de l'Ouest at the University of Angers uses a 2-pronged approach. It combines genotyping (searching for 24 *DPYD* deleterious gene variants by pyrosequencing) with testing for deficient phenotypic status (using uracil and dihydrouracil quantification and the dihydrouracil/uracil ratio as an index of metabolism). In addition, physiologic and physiopathologic parameters are considered.

This multiparametric approach — marketed as ODPM Tox by Onco Drug Personalized Medicine (ODPM), which is based in Angers, France — is superior to just testing for mutations, which misses many people, Dr. Metges noted.

Analysis After Toxicity

In his presentation, Dr. Metges reported data on 247 patients screened only after they had developed severe toxicity (grade 4) or had died after the first cycle of treatment with a fluoropyrimidine-containing regimen.

Only the ODPM Tox test identified all 27 patients who died. Screening for genetic mutations identified only 16 patients (59%) and deficient phenotypic status identified only 24 patients (89%), Dr. Metges reported.

Of the 247 patients who developed severe toxicity, ODPM Tox identified 242 (98%), mutation testing identified 82 (33%), and deficient phenotypic status identified 211 (85%).

Prescreening Saved Lives

The remaining data presented come from prescreening; during the past few years in the Angers region, the test was used before a patient was treated with a fluoropyrimidine.

A total of 11,104 patients were prescreened. Of these, 266 patients (2.4%) were found to have 1 or more genetic mutation, which indicates that they are likely to suffer toxic effects and therefore need a dose reduction or modification.

Two patients were found to be completely PDP deficient — 1 had a homozygote *DPYD2A* and 1 was double mutated, Dr. Metges reported.

"Pretreatment screening saved their lives," he told meeting attendees.

"We are now using this prescreen in routine clinical practice," Dr. Metges reported. He estimated that around 2400 patients are screened annually in cancer centers in the Angers region.

The test is conducted on a single blood sample, and results are available in 8 days. The cost is around €180 (~US\$224) per patient, Dr. Metges said.

A poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium earlier this year ([abstract 410](#)) reported that the cost of prescreening all the new patients in this region of France was less than the cost (in emergency and intensive care costs) of treating severe toxicity in 1 patient. Such prescreening should be recommended before fluoropyrimidine administration, concluded Sory Traoré, MD from the Institut de Cancérologie de l'Ouest, and colleagues.

Linda Celle, marketing director for ODPM, told *Medscape Medical News* that once a person has been identified using ODPM Tox as having a DPD deficiency, another process, ODPM Protocol, is used to modify the dose so it is individualized for each patient. This takes into account patient characteristics (including comorbidities and other drugs being taken); each dose is calculated precisely for a patient's current status, ensuring maximum efficiency and minimizing the risk of toxicity.

Celle explained that when the company is approached by a new medical institution, it works closely with the institution's own molecular laboratory and with physicians treating patients to ensure an efficient flow of information, and provides experts to help with the more complex cases.

14th World Congress on Gastrointestinal Cancer (WCGC): Abstract 0-0019. Presented June 29, 2012.

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